REMARKS

Claims 1-3, 6-12 and 24-30 are all the claims pending in the application; each of the claims has been rejected.

Applicants note that in the Advisory Action dated July 1, 2003, the Examiner states that the Amendment Under 37 C.F.R. §1.116, filed May 9, 2003, will be entered, and that the rejection of the claims under 35 U.S.C. §112, second paragraph has been overcome. The instant Second Amendment Under 37 C.F.R. §1.116 therefore addresses the only outstanding rejection in the application, namely the rejection of the claims under 35 U.S.C. §103.

Furthermore, because the Examiner indicated that the previous Amendment would be entered, Applicants include herewith amendments to the claims based on the entry of the amendments to the claims in the previous Amendment.

Claims 1, 3, 6, 27 and 30 have been amended to more clearly define the crosslinked avidin molecules recited in the claims. Support for this amendment is inherent in the specification. In each description of the biotin-avidin-biotin complex in the specification, it is clear that avidin undergoes cross-linking before it is combined with the biotin molecules. Furthermore, there is no discussion in the specification of any cross-linking taking place other than between subunits of the avidin molecules. Thus, the specification inherently supports the recitation of a biotin-avidin-biotin complex where only the avidin is cross-linked.

No new matter has been added. Entry of the amendment is respectfully requested.

I. Rejection of Claims Under 35 U.S.C. §103

A. At page 4 of the Advisory Action, the rejection of claims 1-3, 6, 7-9, 12, 24, and 27-30 under 35 U.S.C. §103(a) as being unpatentable over Haughland et al., in view of Giese, has been maintained.

The Examiner states that Haughland et al. teaches a biotin-avidin-biotin complex such as that recited in the pending claims, but does not disclose the use of crosslinked avidin. The Examiner further states that Giese provides the missing element of Haughland et al. in that it teaches the use of crosslinked avidin. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the crosslinked avidin of Giese in the method of Haughland et al. because the crosslinked avidin is more stable and has a higher biotin affinity than non-crosslinked avidin.

In response, Applicants again respectfully assert that Giese does not teach or suggest that the crosslinked avidin disclosed therein is more stable, nor does Giese teach that the crosslinked avidin has a higher biotin affinity than non-crosslinked avidin. Therefore, it would not have been obvious to use the crosslinked avidin of Giese in the biotin-avidin-biotin complex of Haughland et al. to arrive at the present invention. In particular, there would have been no motivation to use the crosslinked avidin of Giese in the biotin-avidin-biotin complex of Haughland et al.

As pointed out by the Examiner (page 3, lines 16-21, of the Office Action dated February 11, 2003), Giese teaches the optional performance of a derivatization reaction, for example, crosslinking or modifying of functional groups, in between any of the steps and/or after all of the steps of the multiple layer process comprising successive or repetitive attachment of the protein

and extenders to a surface to build up alternating layers of each to change the properties further, for example, to provide a more complete coverage of the surface, more stability, different functional groups, etc. (see the corresponding discussion in Giese at col. 2, lines 41-47).

Thus, Giese discloses that the stability of the multiple layer comprising successive or repetitive attachment of proteins (such as avidin) and extenders (such as biotin) can be enhanced, for example, by optionally performing a crosslinking treatment. The crosslinking treatment disclosed in Giese is apparently a method which may be optionally carried out for stabilizing the multiple layer as a whole. It is not taught as a method for stabilizing only the avidin by forming an intramolecular crosslinkage.

More particularly, in the crosslinking treatment disclosed in Giese, not only an intramolecular crosslinkage of the protein (such as avidin), but also various crosslinkages (for example, an intermolecular crosslinkage between the proteins, between the extenders (such as biotin), or between the protein and the extender, or an intramolecular crosslinkage of the extender) are formed. Taking into consideration the object of the crosslinking treatment in Giese (i.e., the improved stability of the entire multiple layer), the intermolecular crosslinkage is much more important than the intramolecular crosslinkage of avidin. In addition, the crosslinking treatment disclosed in Giese is a convention method wherein a well-known stabilizing mechanism is used, for example, a method for stabilizing an erythrocyte membrane by treating with aldehyde.

Therefore, Giese simply discloses that the crosslinked multiple layer as a whole is more stable than the untreated multiple layer. Giese does not specifically teach or suggest that the

crosslinked avidin itself is more stable, nor Giese does teach or suggest that the crosslinked avidin has a higher biotin affinity than the non-crosslinked avidin.

Thus, one of ordinary skill in the art would not have expected crosslinked avidin to be more stable and have a higher biotin affinity based on the disclosure of Giese, and therefore they would not have been motivated to use the crosslinked avidin of Giese in the biotin-avidin-biotin complex of Haughland et al., with the expectation of arriving at the improved biotin-avidin-biotin complex of the present application.

To further prosecution of the application, and in view of the Examiner's comment in the Advisory Action at page 3, lines 3-5 from the bottom of the page, Applicants include herewith an amendment to the claims, making it clear that only the avidin is subjected to cross-linking. As discussed above, Giese only discloses that the crosslinked multiple layer as a whole is more stable than the untreated multiple layer. Giese does not specifically teach or suggest the two advantages of crosslinked avidin, namely (1) increased stability of the avidin itself, and (2) higher biotin affinity.

In conclusion, it would not have been obvious to one of ordinary skill in the art at the time of the invention to use the cross-linked avidin of Giese in the biotin-avidin-biotin complex of Haughland et al. to arrive at Applicants' invention. Indeed, there is no motivation or suggestion to combine the two references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At page 6 of the Advisory Action, the rejection of claims 10, 11, 25 and 26 are under 35 U.S.C. §103(a) as being unpatentable over Haughland et al. and Giese, further in view of Tatsumi (U.S. Patent No. 5,843,746), has been maintained.

The Examiner references his comments above on Haughland et al. and Giese, and states that while these references fail to teach a biotin-introduced fused-protein of an enzyme such as a biotin-introduced luciferase, Tatsumi teaches a fusion protein (biotinylated firefly luciferase) which can be applied to a variety of bioluminescent analysis methods. The Examiner explains that such a complex may be bound through the biotin moiety to avidin or streptavidin to form a luciferase complex.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the fused protein of Tatsumi in the combined method of Haughland et al. and Giese for detecting activity of luciferase since Haughland et al. teaches an enzyme immunoassay method of using binding agent-biotin-avidin-biotin-enzyme and the luciferase enzyme of Tatsumi can be biotinylated.

In response, for the reasons stated above, and in view of the amendment to the claims, Applicants assert that the combination of Haughland et al. and Giese does not make obvious the biotin-avidin-biotin complex of the present application. Furthermore, Tatsumi does not cure the defects of Giese discussed above. Therefore, one of ordinary skill in the art would not have been motivated to combine Haughland et al. and Giese to arrive at the biotin-avidin-biotin complex of the present invention, and by extension, they would not have been motivated to further combine the disclosure of Tatsumi to arrive at the invention as recited in the rejected claims.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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